

**AMENDMENTS TO THE SPECIFICATION:**

Please amend the specification by inserting before line 3 on page 1 (i.e., before paragraph [0001] of the published application) the following:

**BACKGROUND**

Please amend the specification by inserting after line 6 on page 4 (i.e., before paragraph [0005] of the published application) the following:

**SUMMARY**

Please amend the specification by inserting after line 10 on page 6 (i.e., before paragraph [0008] of the published application) the following:

**DETAILED DESCRIPTION**

Please replace the paragraph on page 8, beginning at line 9 (i.e., paragraph [0014] of the published application), with the following:

For example, it is possible to use the BLAST program, "BLAST 2 sequences" (Tatusova et al., "Blast 2 sequences - a new tool for comparing protein and nucleotide sequences", FEMS Microbiol Lett. 1/4:247-250) available on the world wide web at <http://www.ncbi.nlm.nih.gov/gorf/b12.html> [ncbi.nlm.nih.gov/gorf/b12.html](http://www.ncbi.nlm.nih.gov/gorf/b12.html), the parameters used being those given by default (in particular for the parameters "open gap penalty": 5, and "extension gap penalty": 2; the matrix chosen being, for example, the matrix "BLOSUM 62" proposed by the program), the percentage of identity between the two sequences to be compared being calculated directly by the program.

Please replace the paragraph on page 15, beginning at line 25 (i.e., paragraph [0041] of the published application), with the following:

According to another aspect, the invention relates to a murine hybridoma capable of secreting a monoclonal antibody according to the present invention, especially the hybridoma of murine origin such as deposited at the Centre Collection National de Culture De Microorganisme (CNCM, National. Center of Microorganism Culture) (Institut Pasteur, 25, rue du Cocteur Roux, F-75724 PARIS Cedex 15 Paris, France) on Sep. 19, 2001 under the number I-2717.

Please replace the paragraph on page 82, beginning at line 4 (i.e., paragraph [0338] in the published application), with the following:

The results presented in figure 7 shown that the MAb 7C10 is capable of significantly inhibiting the growth of the tumor MCF-7 *in vivo* (the asterisks (\*) correspond to the comparison control group/7C10 group in a t-test). In a surprising fashion, the antibody 7C10 seems to be significantly more efficacious than ~~Lamoxifen~~ tamoxifen for the inhibition of the tumor growth (the circles ( ° ) correspond to the comparison tamoxifen group/7C10 group in a t-test) suggesting that this type of treatment by MAB might be substituted for treatment with tamoxifen.

Please replace the paragraph on page 85, beginning at line 22 (i.e., paragraph [0349] of the published application), with the following:

The activity of the inhibition of the IGF1 growth induced *in vitro* on the line MCF-/ ought to be the translation of an inhibition of the transduction of the signal mediated by IGF1 during the attachment of the MAb 7C10 to the receptor. In order to

verify this hypothesis, MCF-7 cells were incubated with or without IGF1, in the presence or in the absence of the antibodies to be tested. After a short incubation time, the cells were ~~lyzed~~ lysed, the  $\beta$  chain immunoprecipitated and the phosphorylation of this subunit estimated with the aid of an antiphosphotyrosine kinase antibody. The results presented in figure 13 show that the attachment of the 7C10 or of the h7C10 significantly inhibits the phosphorylation of the subunit of IGF-IR contrary to an irrelevant murine (9G4) or human antibody (written IgG1 on the scheme).

Please replace the paragraph on page 88, beginning at line 31 (i.e., paragraph [0362] of the published application), with the following:

As indicated above, IGF-IR is capable of ~~confering~~ conferring protection against apoptosis when it is overexpressed on the surface of cells. Furthermore, it has been demonstrated in these examples that the antibodies 7C10 and 7H2HM were capable of potentiating an active compound in chemotherapy. In order to test the power of the antibodies 7C10 and 7H2HM to induce apoptosis, and to explain in part their synergy potential with the chemotherapy, experiments were conducted on the MCF-7 cells in the presence or in the absence of doxorubicin, a medicament known to induce the apoptosis of this cell line *in vitro*. In these experiments, the MCF-7 cells are inoculated at  $2 \cdot 10^4/\text{cm}^2$  in Petri dishes and cultured for 24 h in RPMI without phenol red supplemented with 10% of fetal calf serum (FCS). The cells are then washed twice with PBS and put back into culture in medium with 0% FCS. They are allowed an adaptation time of 10 minutes at 37°C. before the addition of the antibodies at 10  $\mu\text{g}/\text{ml}$ . After an extra 10 minutes. at 37°C, recombinant IGF-I

(Sigma) is added to the culture medium to a final concentration of 50 ng/ml. The cells are left at 37°C again for one hour in order to allow the attachment of the antibodies and of the IGF-I. Finally, the doxorubicin (Sigma) is added to the culture medium at 2 µg/ml and the cells are incubated for 24 hours at 37°C.

Please replace the paragraph on page 95, beginning at line 4 (i.e., paragraph [0383] of the published application, with the following:

As a preliminary step to humanization by CDR grafting, the amino acid sequence of 7C10 VL was first compared with all the mouse VL sequences present in the databank of Kabat (Internet address:

~~[ftp://ftp.ebi.ac.uk/pub/database/kabat/fasta\\_format/](ftp://ftp.ebi.ac.uk/pub/database/kabat/fasta_format/)~~

[ftp.ebi.ac.uk/pub/database/kabat/fasta\\_format/](ftp://ftp.ebi.ac.uk/pub/database/kabat/fasta_format/), last update of data dates from 1999).

7C10 VL has thus been identified as belonging to the subgroup II of the Kappa light chains as defined by Kabat et al. (In *Sequences of proteins of immunological interest* (5<sup>th</sup> edn.), NIH publication No. 91-3242, US Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, 1991). The VL regions of monoclonal antibodies of mice having a sequence identity ranging up to 95% have been identified (DRB1-4.3 (SEQ ID No. 55): 95% and C94-5B11'CL (SEQ ID No. 56): 95%, see figure 17). In order to attempt to identify the out of the ordinary residues in the 7C10 VL sequence, the amino acid sequence of 7C10 VL (SEQ ID No. 54) was aligned with the consensus sequence of the subgroup II of the mouse kappa chains (SEQ ID No. 57) as defined by Kabat (see figure 17).